NTP
National Toxicology Program

NTP Research Concept: Biospecimen Repository and Analysis Capabilities to Support NTP Exposure Assessment Projects

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NIEHS/NTP

NTP Board of Scientific Counselors Meeting
April 13, 2011

Background and Rationale

- Historical use of human exposure information
- Prior and ongoing exposure projects
- Current issues and need for expanded effort

Historical NTP Use of Human Exposure Information

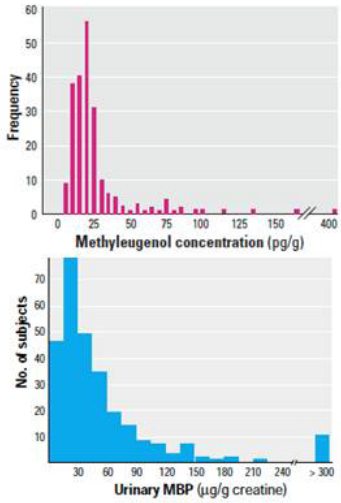
- Guide decisions in selection and design of toxicology studies
  - Relative priority
  - Physical-chemical characteristics of materials of interest
  - Appropriate route of administration
- Targeted assessment activities to provide human health context
  - Comparison of blood levels in exposed rodents and humans
  - Characterization of workplace exposures
- Types of exposure information
  - Indirect measures ("exposure potential")
    - Production and use, environmental release, levels in products and media
  - Direct measures
    - Exposure studies, biomonitoring surveys

Prior and Ongoing Exposure Projects

- General population biomonitoring
- Workplace exposure characterizations
- Small targeted population studies

Prior and Ongoing Exposure Projects (1)

General population biomonitoring



- CDC/NCEH Interagency Agreement
- Biospecimens from a subset of NHANES III
- Methyleugenol
  - Barr et al. *Environ. Health Perspec.* 2000
  - Schecter et al. *Environ. Health Perspec.* 2004
- Phthalates
  - Blount et al. *Environ. Health Perspec.* 2000
  - Kohn et al. *Environ. Health Perspec.* 2000
  - Koo et al. *Environ. Health Perspec.* 2000
- Phytoestrogens
  - Valentin-Blasini et al. *J. Exp. Anal. Environ. Epidemiol.* 2000, 2003

Prior and Ongoing Exposure Projects (2)

Workplace exposure characterizations

- NIOSH Interagency Agreement
  - Bisphenol A
  - Engineered nanomaterials
  - Diacetyl/food flavorings
  - Indium compounds
  - Welding fume/manganese
  - Recent NTP toxicology study nominations
    - 2-Methoxy4-nitroaniline
    - ***p-Chlorobenzotrifluoride***
    - Ethylene glycol 2-ethylhexylether
    - 2',2'''-Dithiobisbenzanilide
    - ***Tungsten oxides***

Journal of Occupational and Environmental Hygiene, 5: 463–474
ISSN: 1545-9624 print / 1545-9632 online
DOI: 10.1080/15459620802214792

Presence of Airborne Fibers in Tungsten Refining and Manufacturing Processes: Preliminary Characterization

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In tungsten refining and manufacturing processes, a series of tungsten oxides (WO_3) are typically formed as intermediates in the production of tungsten powder. Studies in the Swedish tungsten refining and manufacturing industry have shown that intermediate tungsten refining processes can create WO_3 fibers. The purpose of the present study was to identify and provide a preliminary characterization of airborne tungsten-containing fiber dimensions, elemental composition, and concentrations in the U.S. tungsten refining and manufacturing industry. To provide the preliminary characterization, 10 static air samples were collected during the course of normal employee work activities and analyzed using standard fiber sampling and counting methods. Results from transmission electron microscopy analyses conducted indicate that airborne fibers with length >0.5 μm, diameter >0.01 μm, and aspect ratio ≥3:1, with a geometric mean (GM) length of ~2.0 μm and GM diameter of ~0.25 μm, were present on 9 of the 10 air samples collected. Energy dispersive X-ray spectrometry results indicate that airborne fibers prior to the carburization process consisted primarily of tungsten and oxygen, with other elements being detected in trace quantities. Results from an air sample collected at the carburization process indicated the presence of fibers comprised primarily of tungsten with oxygen and carbon, and traces of other elements. Based on National Institute for Occupational Safety and Health standard fiber counting rules, airborne fiber concentrations ranged from below the limit of detection (<0.1 f/cm³). The calcining process was associated with the highest airborne fiber concentrations. More than 99% (574/578) of the airborne fibers identified had an aerodynamic diameter ≤3.0 μm, indicating that they were capable of reaching the thoracic regions. Until more is known about the durability and potential health effects associated with airborne tungsten-containing fibers, it would be prudent to take steps to limit or eliminate occupational exposures.

Keywords electron microscopy, hard-metal manufacturing, occupational exposure, thoracic, tungsten blue oxide, tungsten oxide bronze

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The findings and conclusions in this report are those of the author(s) and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

INTRODUCTION

Tungsten (W) is a naturally occurring element that can be refined and alloyed in production processes to provide products with unique physical and chemical properties well suited to industrial applications. For example, tungsten alloys tend to be strong and flexible, resist wear, and conduct electricity well. Tungsten and its alloys are used as light bulb filaments, as the target anode in X-ray tubes, as catalysts for chemical reactions, as a component of steel in high-speed tools, as welding electrodes, and as gyroscope wheels. Sintered mixtures of tungsten carbide and other metals, referred to as cemented tungsten carbide or hard metal, are the most common tungsten products produced.[1] Because of the numerous and diverse applications of tungsten in industrial and commercial products, it is estimated that in 2002, approximately 800,000 workers potentially came into contact with or were exposed to tungsten compounds in ~50,000 workplaces throughout the United States.[2] Approximately 4500 of these workers are potentially exposed to tungsten in the refining and manufacturing industry.[2]

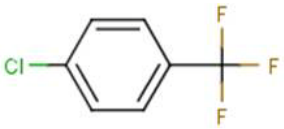
The purpose of the present study was to identify and provide a preliminary characterization of dimensions, elemental composition, and concentrations of airborne tungsten-containing fibers in the U.S. tungsten refining and manufacturing industry.

Tungsten Oxides

- Nominated for NTP testing in 2004 based on presence of potentially hazardous fibrous particles in certain manufacturing scenarios
- NIOSH project objectives:
  - Determine if tungsten oxide fibers are present in tungsten refining and manufacturing processes in US
  - Characterize dimensions and concentration of airborne fibers
  - Assess durability of tungsten oxide fibers
- Accomplishments:
  - Respirable tungsten oxide fibers of > 3:1 aspect ratio found in two manufacturing facilities, concentrations low and few workers exposed (McKernan et al. *J. Occup. Environ Hyg.* 2008; *Ann. Occup. Hyg.* 2009)
  - Tungsten oxide fibers dissolved more slowly than tungsten metal and/or tungsten trioxide in artificial lung fluids (Stefaniak *Part. Fibre Toxicol.* 2010)
  - Dimension, dose, durability, and number of workers exposed did not warrant additional investigation

PCBTF (1-Chloro-4-(trifluoromethyl)benzene)

- Nominated for NTP testing in 2009 based on increasing use and lack of chronic toxicity data
- NIOSH project objectives:
  - Identify producers, formulators end-users
  - Identify and compare appropriate sampling methods
  - Measure representative exposures to inform toxicity testing
- Current status:
  - 3 air sampling methods evaluated
  - 3 paint manufacturers, 1 end-user (furniture glue solvent) agreed to participate
  - 2 site visits completed



Prior and Ongoing Exposure Projects (3)

- Small targeted population studies
  - NIEHS Clinical Research Unit
  - Bisphenol A
    - Exposures from thermal paper in cashiers
    - Oral elimination kinetics in volunteers

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Cashiers may face special risks from BPA

The concern: Pregnant ones may transmit the pollutant to their babies

By Janet Raloff
Web edition : Monday, August 2nd, 2010

Text Size

National Toxicology Program

Bisphenol A (BPA)

Current Issues and Need for Expanded Effort

- Limitations of existing human exposure information
  - Incomplete information on combined exposures and common mixtures
  - Difficulty in tracking emerging substances of concern
- Institutional focus on developmental basis of adult disease
  - Growing recognition of potential influence of early life exposures on cancer, asthma, obesity, diabetes, neurological development, etc.
  - New HHS or Cross Department Government Initiatives
    - e.g. President's Children's Environmental Health and Childhood Obesity Task Forces
- NRC Committee on Human and Environmental Exposure Science in the 21st Century
- Follow up on research recommendations from NTP Workshops
  - Diabetes and Obesity (January 2011)
  - Chemical Mixtures (September 2011)

Specific Aims

- Develop a mechanism for accessing resources of banked human biospecimens that could be used to rapidly address focused questions of relevance to NTP programs
  - Expanded NTP literature analysis activities
  - High throughput screening activities of Tox21
- Perform targeted analyses of agents of emerging public health concern
  - Is there exposure?
  - What are important routes of exposure?
  - Are there common co-exposures?
  - Do the exposures provide support for further NTP evaluations/studies?
- Address specific hypotheses regarding exposure-health outcome associations
  - Identify putative associations that are worthy of additional NTP investigation
  - Can these associations be confirmed or refuted by targeted analyses of human biospecimens?

Proposed Approach

- Identify relevant existing resources to create a virtual network of biospecimen repositories
  - Engage NCEH and other federal partners regarding availability of biospecimens
  - Inventory existing biospecimen repositories assembled as part of ongoing or past research supported by the extramural grants programs of NIEHS or the National Institute of Child Health and Human Development
    - Identified ~70 biospecimen banks collected and maintained via NIEHS grants
    - Engage NIH-supported extramural investigators
- Utilize contract analytical chemistry capabilities or interagency agreements with federal partners for sample analysis

Existing NTP Capabilities and Options

- NIEHS Clinical Research Unit
  - Biospecimens from Sample Collection Registry
  - New studies
- Storage of biospecimens
  - Physically housed within NTP Archives
- Analytical chemistry
  - NTP chemistry support contracts
  - FDA/NCTR Analytical Chemistry Unit
  - CDC/NCEH Division of Laboratory Sciences

Scope

- Specific project design based on hypotheses to be addressed
  - Up to several projects per year
- Focus on general population exposures
  - Men and women in prime reproductive years, children
- Types of biospecimens
  - Primarily peripheral blood and urine; also cord blood, amniotic fluid, breast milk, saliva, hair, nails, cells (buccal, PBMC)
- Types of studies
  - Cross-sectional or longitudinal
  - Repeated biospecimen sampling preferred
  - Other exposure assessment methods preferred
  - Start with NIH-funded
- Types of analyses
  - Primarily parent chemicals or metabolites for exposures of interest
  - Potential for biomarker discovery/validation (exposome)

Biospecimen Bank Examples

- Pilot study of environmental exposures in Danish women (NICHD)
  - Hatch, Boston University and Sorensen, Aarhus University Hospital
  - Urine and blood from 50 women prior to pregnancy and twice during pregnancy
- Endocrine disruptors and fetal development (NIEHS)
  - Padmanabhan, University of Michigan
  - Repetitive sampling of blood and urine during pregnancy
  - Cord blood, placenta and cord samples at birth
  - ~1000 samples collected to date
- SEARCH for Diabetes in Youth (CDC, NIDDK)
  - Multicenter study of children with type 1 or 2 diabetes
  - Blood and urine collected from ~ 9,000 children
- University of California at San Francisco
  - Local outpatient clinic; diverse patient population
  - Serum collected from second trimester pregnant women

Significance and Expected Outcome

- Enhance the NTP's exposure assessment capabilities
- Provide an additional set of tools useful for putting findings from toxicology studies and literature analysis activities into human health context
- Gain access to resources that contain repeated measures of blood and urine from men and women of childbearing age, women who are trying to become pregnant, and women during pregnancy and lactation
- Improve our ability to identify environmental exposures that are most worthy of public attention

Questions for the Board

- Rationale for proposed research program
- Merit relative to the mission and goals of the NTP
- Significance and public health impact
- Scope
- Other thoughts

Some Definitions

Exposure : Concentration or amount of a particular agent that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration (IPCS 2002)

Exposure assessment: The process of estimating or measuring the magnitude, frequency and duration of exposure to an agent, along with the number and characteristics of the population exposed. Ideally, it describes the sources, pathways, routes, and the uncertainties in the assessment (IPCS 2002)

Exposure information: Anything that informs the above

Biological monitoring or biomonitoring: Measuring chemicals in biological materials (blood, urine, breath, etc.) to determine whether chemical exposure in humans, animals, or plants has occurred (ATSDR 1999)